MICROSTIMULATORS AND MICROTRANSDUCERS FOR FUNCTIONAL NEUROMUSCULAR STIMULATION

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Abstract:

Standard operating procedures for assembly and quality-control testing of the glass packaged BIONs were finalized and implemented. Manufacturing yields exceeded 90%. A qualification test plan was developed and executed in preparation for clinical tests of the BION1 implants scheduled to begin this spring at Queen's University. BIONs were subjected to a wide range of mechanical, thermal and electrical stresses simulating worst-case use and accelerated life conditions. They were tested repeatedly for integrity of mechanical form, hermetic seals and electrical function. All tests were passed. Long-term testing has been extended past the requirements.

Electronic subassemblies incorporating the new ASIC and ceramic PCB have been built and successfully tested, although some yield problems remain to be resolved. These subassemblies have been built successfully into completed glass capsules that now include the water-getter and have passed hermeticity testing.

Front-end ASICs were built and tested at IIT to determine the rules and specifications for the bidirectional telemetry capabilities of the BION2. A communications protocol based on those rules was developed and approved. A new version of the bedside controller has been designed and is under construction at Queen's University. It will be capable of producing the synchronous modulation sequences required for both the present 2 MHZ AM encoding scheme and the 470 kHz suspended-carrier encoding scheme.

Second generation ASIC's were received and tested. Phil Troyk at IIT discovered a circuit cut out problem that occurred at certain magnetic field strength and certain depths of modulation. In a special test for this problem at AEMF, a 15% loss of die was found. A modification of the circuit to cure this problem is in progress.

ITEMS APPENDED:
1 annotated color photograph of BION1 implant
Qualification Test Report for BION1 System (Mar. 25, 1999)
Qualification and final test burn in procedures were developed specifically for human implant.
BIONish Universal Communications and Command Protocol (final draft Dec. 14, 1998)
BION Personal Trainer design document (Jan. 4, 1999, rev. April 15, 1999)

Microstimulator Yields

As mentioned in the last report, yields during fabrication of electronic subassemblies for BION1 Microstimulators have been disappointing, on the order of 40% good units even starting with tested chips. A major yield hit occurs when the top ferrite hemi-cylinder is attached to the surface of the die. In an effort to reduce losses, a different attachment epoxy was tried. Slight (possibly random) improvement was observed, but yields remained disappointing at that step. It is hoped that additional nitride passivation (see below) will improve the handleability of the chips.

Another source of failure has been traced to testing differences between Pritzker Institute and the Mann Foundation. Chip and assembly tests at the Mann Foundation were run with the lower of the two carrier levels set at about 80% of the higher level, while the tests at the Pritzker Institute used a lower level of 90%. As a result, some stimulators showed failures to communicate under some signal conditions, while others worked properly. At root, this problem is most likely due to high offset voltage in a comparator in the Microstimulator data detector circuit. This comparator can be re-designed to reduce offset voltage variations, but that will require a completely new set of fabrication masks. The solution is to either modify the tests at the Mann Foundation to use reduced modulation or to use the greater depth of modulation with all the units. Ten percent of the units needed the greater depth of modulation to function.

Dedicated Wafer Run

As previously reported, metal mask errors made some BION2 test chips on the dedicated wafer run unusable. Wafers with the metal layer corrections were received from the foundry and have now been sent out to have additional silicon nitride passivation added to improve their in-process durability. We are awaiting the arrival of these wafers.

Production Testing, Final Acceptance Tests and Qualification Burn In Testing:

AEMF is providing additional funding to develop the production testing, final acceptance testing, and qualification testing, specifically for human use. Burn in jigs, fixtures, temperature cycling ovens and other test equipment is being constructed and purchased. The most critical test is a 1000 hour powered burn in of the electronics modules at 125EC.

About 80 electronics modules have been constructed for initial functional biocompatibility and corrosion testing. Approximately 20 were shipped to Queens for construction into glass cases. The others will be used in tests at AEMF. These 80 units can't be burned in because the insulation on the copper wire used for the coil winding could not tolerate 125EC. Additional units with high temperature insulated wire are being constructed for the 1,000 hour burn in.

Prior to the 1,000 hour qualification powered burn in, the units must pass a full electrical test before and after a 72 hour powered burn in. This is the standard 100% final production test.

Final Report of Work Done at Queen's University

Work at Queen's University has continued with funding from the Medical Research Council of Canada. In the last quarter, we have concentrated on preparing the regulatory submission for a clinical trial of BIONs in which therapeutic electrical stimulation (TES) will be used to prevent and/or reverse atrophy of shoulder muscles and subsequent painful subluxation of the shoulder joint in stroke patients. This was submitted on May 12, 1999, to the Therapeutic Products Program of Health Canada. Most of the support material has been presented in previous QPRs of this contract.

Fabrication of BION1 Implants

The new ASIC was built into electronic subassemblies using the new ceramic PCB at AEMF. The subassemblies were tested for RF field strength and modulation sensitivity at IIT and sent to Queen's for packaging. These new electronic subassemblies required slight changes to the glass package used to date for the old electronic subassemblies, which were based on an epoxy PCB. In particular, the glass capillary tube for the capsule subassembly is now .030@ shorter and the spring that extends from the tubular feedthrough subassembly to the ceramic PCB is straight rather than tapered (see BION1 annotated photograph).

We have also begun to incorporate the water getter into the packages, which we omitted during qualification testing in order to increase sensitivity to any trapped or leaking water vapor. The getter consists of 70% anhydrous magnesium sulfate in a silicone elastomer that is molded into a tube .020@ i.d. x .060@ o.d. and cut into .040@ thick slices. The getter cylinder slips over the spring and sits between the PCB and the glass bead that is sealed to the tubular feedthrough. The getter is subjected to fairly high temperatures when the glass capsule is closed by melting the open end of the glass capsule subassembly to the glass bead on the tubular feedthrough. If the getter is not completely anhydrous, the heat tends to cause it to release some water vapor into the capsule. The water vapor is quickly reabsorbed by the getter, but it is desirable to prevent the possibility of condensation occurring even temporarily. Keeping the getter in a desiccator is not as effective as we had hoped because the magnesium sulfate itself is as effective a desiccant as the desiccants commonly available, so a small volume of getters may actually wind up absorbing water from a large volume of desiccant. Instead, we are now baking out the magnesium sulfate before curing into the silicone and storing the cured getters until needed in an oven at 230C, close to the maximal temperature before discoloration occurs.

The completed and sealed BION1 implants have passed the standard production tests described in the appended Qualification Testing report including hermeticity and anodization, but not the 72 hour powered burn in, or the 1,000 hour qualification test. In particular, 11/12 survived the 24 h high pressure bomb test (160 atm in saline) which effectively weeds out units with latent microcracks or stress risers in the glass seals, as described previously (QPR #14). Complete electrical function testing and long-term temperature cycling and active pulsing await the delivery from IIT of the new coil-drivers matched to the properties of the new ASICs.

Qualification Testing of BION Implants

The complete Qualification Test Plan and Report are appended. These tests deal mostly with the mechanical integrity and hermeticity of the glass package, so they were performed on units with the old electronic subassembly and without getters. As of this writing, the following long-term tests are still underway, with interim results indicated:

Chronic high pressure bomb: 2 units started on test Jan. 4; 8 started Feb. 17. 8/10 still on test as of April 20; 1 from each group developed cracks as a result of rough handling during weekly removal from test fixture and examination for condensed moisture. These tests will continue indefinitely. We have room for 16 total units in the high pressure bomb fixture and we are making a second fixture for the 24h production testing to reduce handling of the devices on long-term testing.

Chronic temperature cycling and active pulsing: 3 units started Feb. 17, all still functioning as of April 20 (62 days). 8 units started Oct. 5, 1998 without 24h high pressure bomb test; 5 still on test (197d), 2 cracked (at 42d and 51d) and 1 removed to make room for new devices. All 8 test wells are now occupied with old BIONs; all will be removed to make room for 8 BION1s with the new ASIC and electronic subassembly and getter as soon as they complete production testing.

Chronic moisture sensing by impedance spectroscopy: 4 units started on test in 80C saline on Nov. 20, 1998; 4 units still on test as of April 20 (150d) with no detectable change from control Bode plot (methods described in QPR #15). We estimate that this test would reveal water condensation at 10-50 monolayers on the PCB surface. The absence of detectable condensate after 5 months at elevated temperature in a largely empty capsule with no added gettering capability is very encouraging; this test will continue indefinitely.

The short-term Qualification Testing focussed on thermal and mechanical stressing of the glass seals, including repeated autoclaving and freezing, dropping of completed BIONs onto hard surfaces, and pushing them axially into meat to simulate insertion. We were able

to do these tests successively on the same set of 5 BIONs without any failures. We also tested the individual hermetic seals in half-capsules by loading them axially while monitoring them for hermeticity at the limits of our helium leak sensitivity ($2x10^{-11}$ cc atm/s). There were no detectable leaks at 1200 g force (>5 times the mean peak insertion force), at which point the o-ring seals of our leak-test fixture could no longer hold the test capsules in place.

Communications Protocol for Bidirectional Telemetry

Previous work under this contract and its predecessor developed the rationale for using simplex transmission in which the RF power transmission from the external, primary coil is shut down while sensing and back-telemetry functions are in operation. The suspended carrier design makes it possible to cut off and reestablish full RF power within 1-2 carrier cycles without dissipating significant energy. This is done by opening the RF tank circuit just as the energy storage in the capacitor reaches its peak and the inductive field strength drops to zero. This 100% modulation is also effective and efficient for transmitting data at a high bit rate. Work at IIT identified the design rules for receiving data encoded by the suspended carrier and for generating an amplitude-modulated outgoing carrier on the same implant (secondary) coils.

The appended document on BIONish$ describes in detail the various clinical applications requirements intended to be serviced by bidirectional telemetry. It formulates a complete data transmission protocol that would meet these needs within the design constraints of the suspended carrier system, as they are presently understood. While there are likely to be changes as the design rules are tested more completely and specific clinical applications are more fully defined, this document does serve two immediate purposes:

It provides a benchmark of likely achievable performance that demonstrates the utility of the suspended carrier transmission system for demanding FES applications.

It provides a common specification that the design teams can incorporate into test ASICs (at IIT) and external control and test hardware (at QU) that are being developed separately.

Potential Problem With Simplex Transmission as a Communication Method

If 50% of the Bions are sensor Bions and need to continuously send out telemetry data, it will require that powering of the other Bions will be significantly reduced, perhaps to the point of not operating. To handle multiple continous sensing functions the Alfred E. Mann

Foundation has funded a separate project to provide full duplex biotelemetry with essentially simultaneous multiple channel back telemetry.

Redesign of the Bedside Controller

The presently available bedside controllers were built several years ago and are unnecessarily bulky and complex, particularly for patient use. They have been used effectively for *in vitro* and *in vivo* preclinical testing of simple stimulation functions, but they do not have the flexibility to support arbitrary carrier modulation sequences such as will be required by the suspended carrier communications protocol that supports the BION2 architecture (BIONish protocol appended).

The BION Personal Trainer$ document (appended) describes a new design for the bedside controller that greatly simplifies its hardware and firmware design. Basically it operates like a giant shift register, sending out modulation states serially to the coil-driver while maintaining synchronization with the carrier frequency. The same bedside controller can be used interchangeably with both the 2 MHZ AM and 470 kHz suspended-carrier modulation schemes.

This mode of operation requires substantial changes to the ClinFit software developed for monitoring and programming BION implant function (described in detail in ClinFit Users Manual appended to QPR #6). In particular, firmware in the microcontroller of the old bedside controller computed the command data from stimulus pulse parameters; the command words were then converted to serial modulation sequences by a field programmable gate array (FPGA). These computations must now be built into the ClinFit software, which downloads a string of carrier modulation states into the memory-backed RAM attached to the 68HC11 microcontroller in the Personal Trainer. The ClinFit software will be upgraded to Visual Basic 5 and will be internally redesigned to reflect a more object-oriented architecture, but its basic functionality and graphic user interfaces will stay the same.

The actual implementation of the new hardware/firmware/software designs has been contracted by Queen's University to Aztech Associates, Inc., of Kingston, Ontario, with partial funding from Advanced Bionics Corp.

Final Report of work done at the Pritzker Institute

During this contract, progress was made in three key areas: concept design for a bidirectional telemetry system based upon suspended-carrier modulation, ASIC design and testing of suspended-carrier front end circuits, and a revised 2MHz transmitter design that uses low-level power Fets and AC-type logic.

Suspended-Carrier Telemetry Concept

Figure 1, below, illustrates the concept of the suspended-carrier method for inward telemetry.

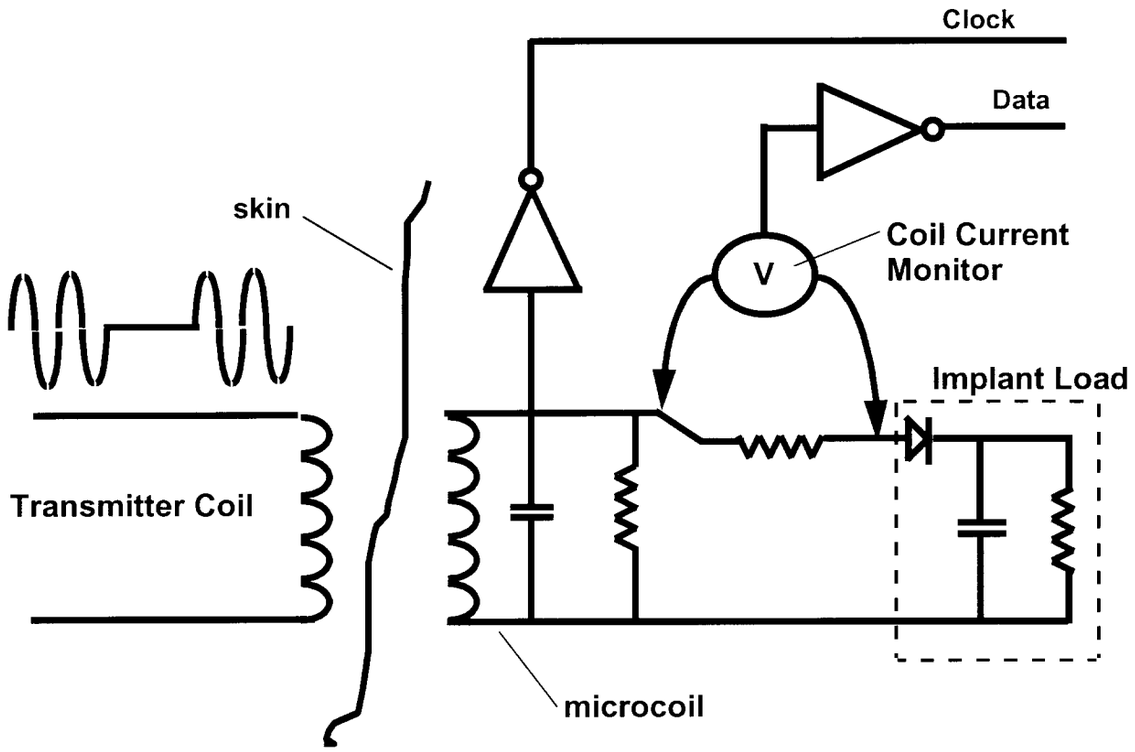


Figure 1 – Concept of suspended-carrier inward telemetry combined with rectification. (simplified schematic)

By sensing current in the rectifiers, rather than coil voltage, the bandwidth of the inward telemetry does not depend upon the Q of the microcoil. In practice, the current sense is accomplished by current mirrors that sense the current in the rectifiers.

Outward telemetry is accomplished by turning off the transmitter and maintaining it in a "suspended" state. Then a local oscillator, within the microstimulator, is turned on. The frequency of the oscillator is determined by the self-resonant-frequency of the microcoil. Therefore the frequency of the oscillator is optimized for the transmitter/microcoil inductive link.

ASIC Design and Analysis

A significant portion of our efforts, during the contract, was spent in examining fully integrated rectification and bidirectional telemetry circuitry targeted for use in combined stimulator/sensor micromodules. During rectification, an integrated bridge structure, comprised of lower n-Fets and upper p-Fets, shown in Figure 2, below suffers from parasitic current in a vertical bipolar transistor. Typically, the p-fet well would be tied to the positive power supply. Since the base of the vertical bipolar is the nwell, forward bias of the p+ regions of the p-fets results in bipolar collector current. This has the effect of pulling current from the power supply. In order to avoid this situation, we devised a bridge that used a floating nwell for the upper p-fet transistors. This approach was highly successful. However, testing of our first-generation test chips revealed a more elusive parasitic mechanism.

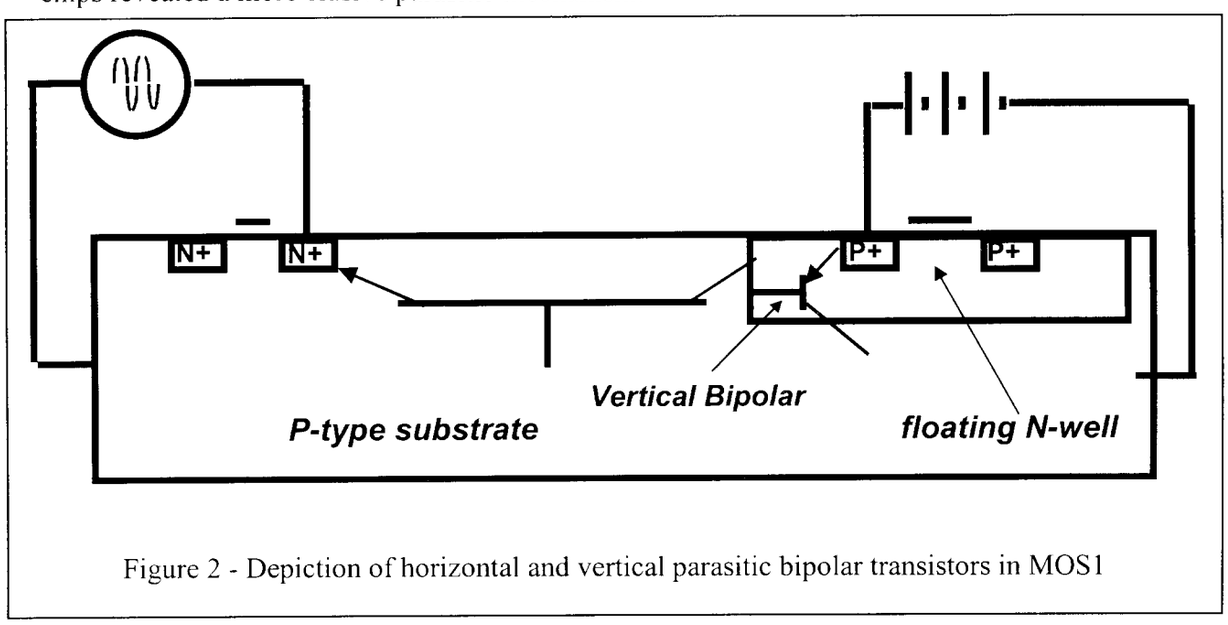


Figure 2 - Depiction of horizontal and vertical parasitic bipolar transistors in MOS1

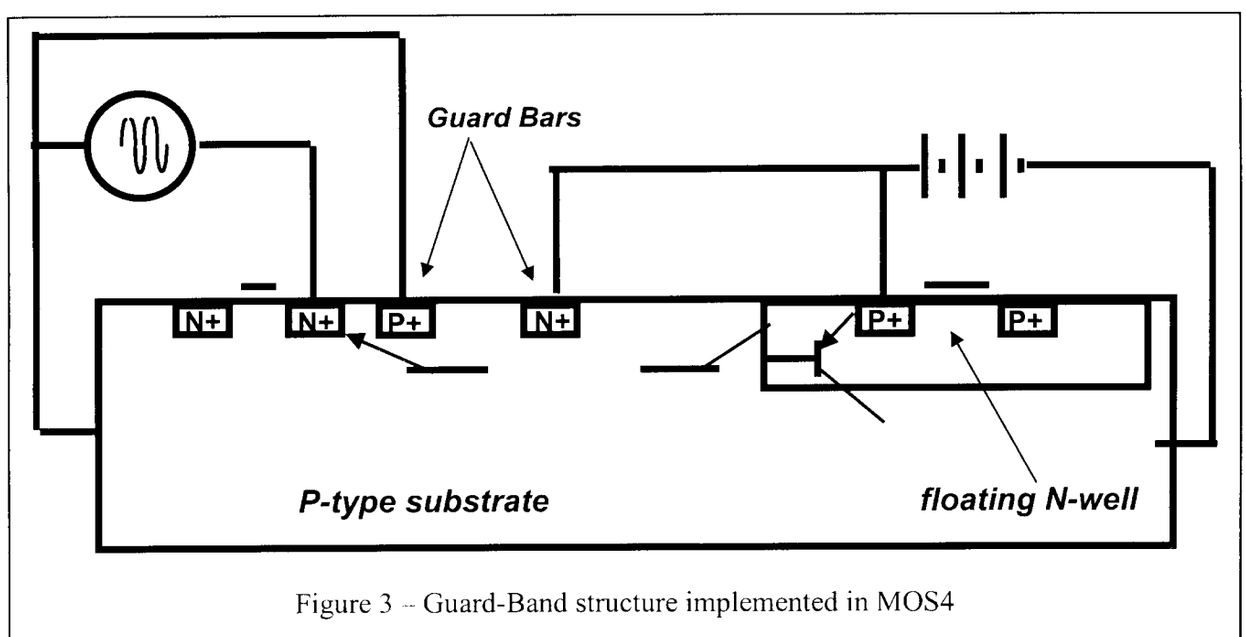


Figure 3 – Guard-Band structure implemented in MOS4

In Figure 1, above, one can see that rectification current in the lower n-fets will forward bias the base-emitter junction of the horizontal bipolar. Current in the horizontal bipolar flows from the power supply, via the floating well, to the substrate. The current will increase until the gain of the horizontal bipolar equals approximately unity. At that point the power supply voltage can no longer increase since all additional current is simply shunted to the substrate. Therefore we attempted to eliminate the horizontal bipolar current using a series of guard bars, in ASIC MOS4, as shown in Figure 3, above.

Unfortunately, this guard structure did not solve the parasitic problem. In addition, the bridge design in MOS4 used newly-sized transistors for the lower rectification elements which caused increased current to flow in the parasitic transistors.

Measurements of MOS4 showed that the parasitic effects were not reduced from that which we had measured in MOS1. We then spent considerable time measuring MOS4 using a combination of laser trace cutting, internal circuit probing, and curve tracer measurements. The layout used 16 sequential substrate and power supply guard-bands to isolate the floating well from the substrate current of the lower rectifier N-Fets.

To some degree, the guard-bands did isolate the floating well. However, this isolation was not effective in preventing the substrate current from reaching other wells, which were part of the guard structures and connected to the power supply. We did confirm that the gain of the horizontal NPN transistor was less than 1, about 0.8. However, even a gain of less than unity results in excessive power-supply-to-substrate currents. Consider that the rectification current which flows in the N+/Psubstrate junctions is also emitter current for the NPN transistor, as shown in Figure 4, below. Collector current, in the NPN transistor, causes power-supply-to-substrate current to flow. Transistor gain rises with increasing collector current. When the collector current of the parasitic NPN transistor plus the ASIC power supply load current equals the maximum available current from the bridge source (implant coil), the power supply no longer increases no matter what the level of source current to the bridge. For MOS4 this value was about 4 volts.

Since the guard-band structure consisted of alternating substrate diffusions and N-wells, we had guarded the floating well, at the expense of creating more NPN parasitic transistors. In retrospect the creations of these new transistors was obvious. However, our attention was focussed upon diverting the current from the floating well. Previously we did not appreciate the impact of the horizontal NPN transistor alone, even though its gain is unity or below. Although we did create these new parasitic transistors, this structure was an improvement over the MOS1 structure in which substrate current reached the floating well. Substrate current which reaches the floating well is further multiplied by the gain of the vertical PNP parasitic transistor contained within the well. However, the improvement is insufficient to avoid a significant drain on the power supply. This situation is shown in Figure 4, below.

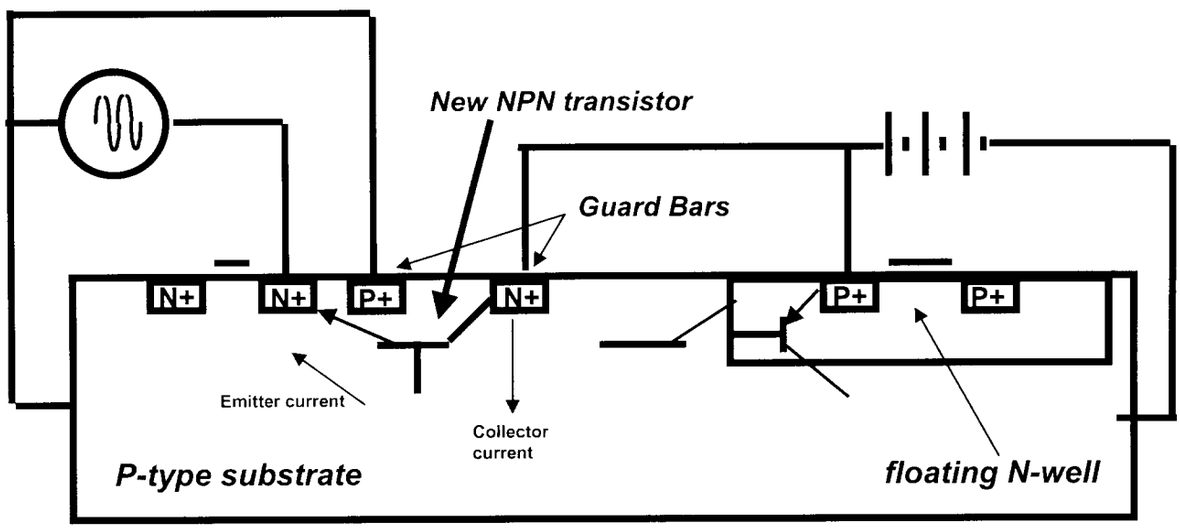


Figure 4 – New parasitic transistor created by addition of guard bands. Although substrate current is blocked from the floating well, the new transistor causes a drain on the Power Supply.

We expended much effort to understand the precise mechanisms of the new parasitic bipolars, to measure their gain, and to understand the geometric significance of the spacing between the guard-bands. Based upon these measurements we identified a new strategy that eliminates all parasitic current. The MOS4 design used synchronous rectification for the upper P-Fet rectifiers. We now intend to use synchronous rectification on the lower N-Fet rectifiers, and increase the size of the N-Fets so that during conduction the forward voltage drop across these N-Fet rectifiers will be so low that no significant current will flow through the emitter-base junction of the parasitic NPN. This is the strategy shown in the Figure 5, below. In addition, we have used one large substrate guard-band surrounding the rectifier N-Fets, and one large N-Well guard-band surrounding the rectifier P-Fets.

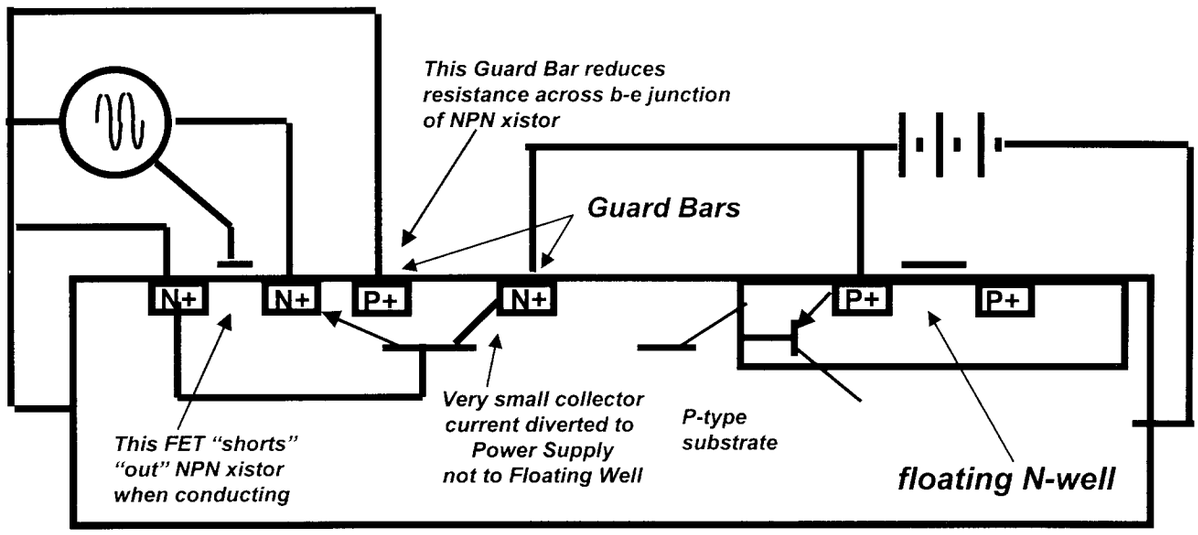


Figure 5 – Strategy for eliminating parasitic rectifier current. When the N-Fet is conducting, the voltage drop across the b-e junction of the NPN is insufficient place it into conduction.

A layout for circuitry that used this technique was completed and sent for fabrication. We have also included the inward telemetry data detection, the clock recovery, and the local oscillator for outward data telemetry. A color plot of this layout, for the chip MOS8, can be seen in Figure 6, below.

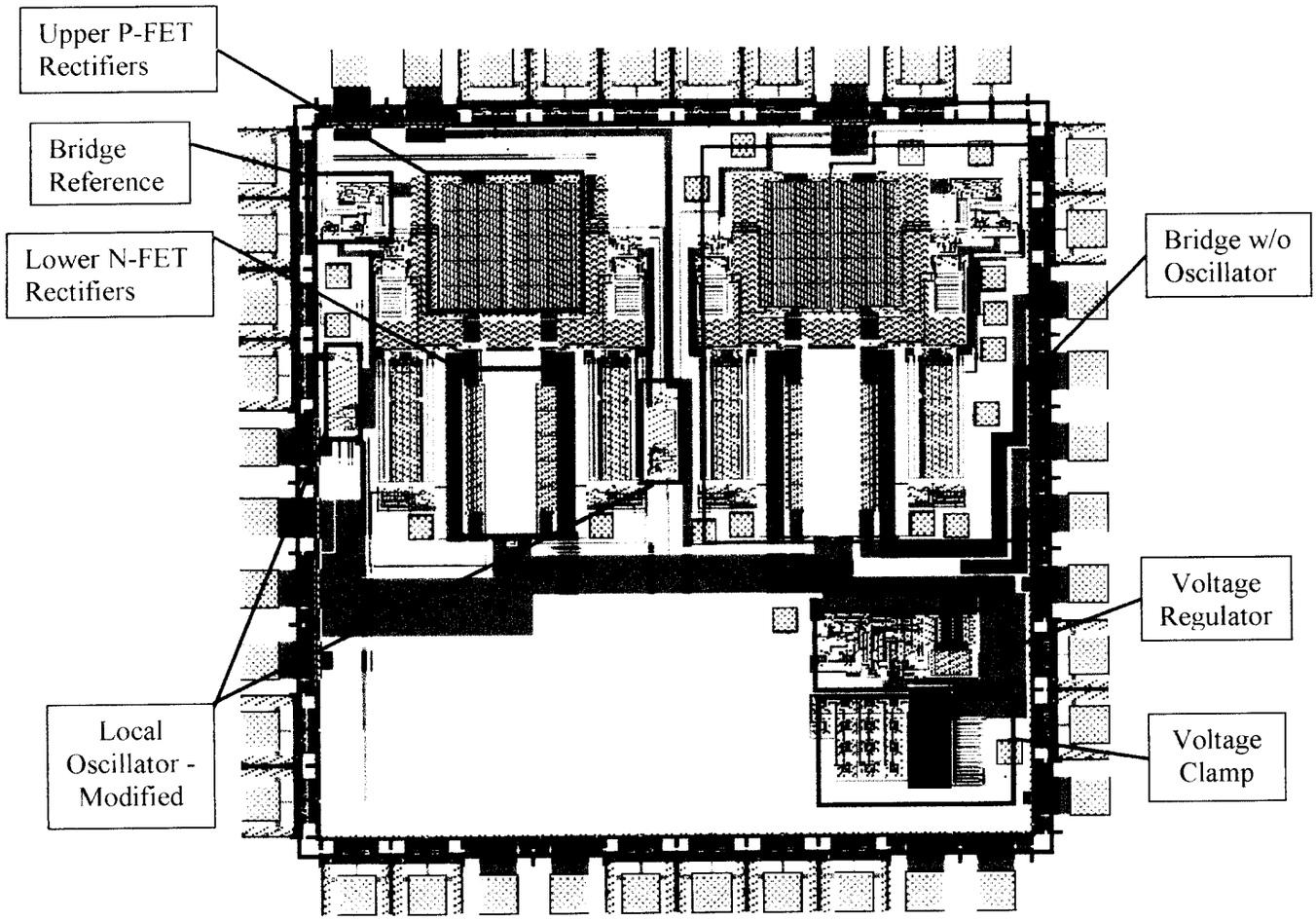


Figure 6 – Color layout of MOS8, ASIC incorporating rectification and bidirectional telemetry in a single front-end design.

Figure 7, below, shows oscilloscope waveforms of the suspended-carrier data demodulator, of MOS8, in operation. Trace 3 is the transmitter coil current. Trace 4 is the modulation command signal. The modulation pattern is 4 cycles on, and 1 cycle off. The data demodulator senses the full-wave rectification current. The output of one phase of the data demodulator is shown in Trace 2. Note that 3 of the 4 carrier cycles are correctly sensed by the demodulator. The first ½ cycle of the rectification current is often missed due to the need to restore energy to the implant coil. Therefore, 4 cycles on , 1 cycle off, typically appears to the data demodulator as 3 cycles on, 2 cycles off. Trace 1 is the recovered clock signal. Note that the clock is correctly recovered even during the cycle for which the transmitter is turned off. This is because the clock recovery circuit functions by sensing the implant coil voltage. When the carrier is suspended the Q of the implant coil allows for a detectable voltage signal even when the rectifiers turn off.

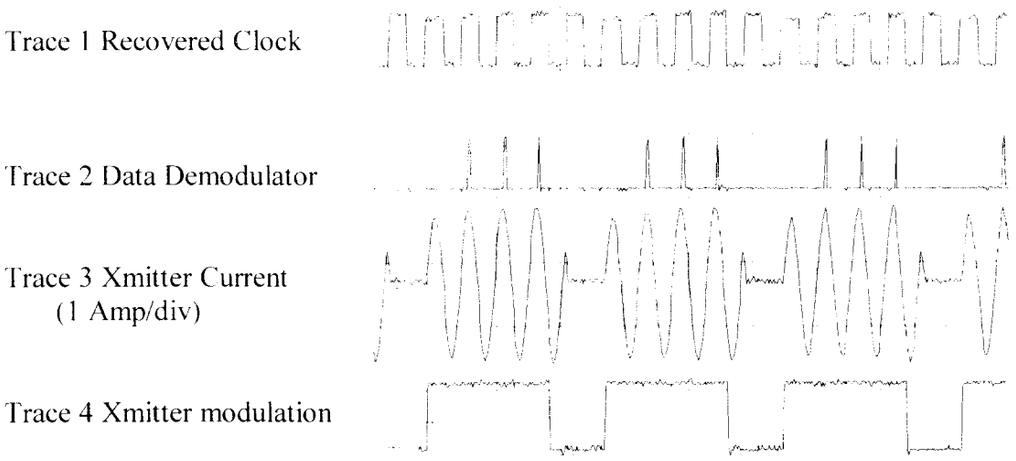


Figure 7 – Data demodulation produced by MOS8, 1usec/horizontal division

In Figure 8, below, the operation of the local oscillator can be seen. Trace 1 shows the implant coil voltage during a period of steady-state transmitter operation and immediately following the suspension of the transmitter. Trace 2 shows the modulated transmitter current. Note that during the time in which the transmitter is turned off, the local oscillator begins operation. This can be verified by observing the amplitude modulation of the local oscillator during the transmitter-off period. For demonstration purposes, the local oscillator is being modulated with a simple on-off pattern.

For purposes of comparison, Figure 9 shows the implant coil voltage without the local oscillator being turned on. Note that, during the transmitter-off period, the coil voltage drops to a low, decreasing, peak level. This voltage level is maintained by the stored energy in the coil. The Q of the coil is sufficiently high so that the tank circuit continues to ring. It is this signal which is detected by the clock recovery circuit, so that normal clocking could be maintained even during periods of transmitter suspension.

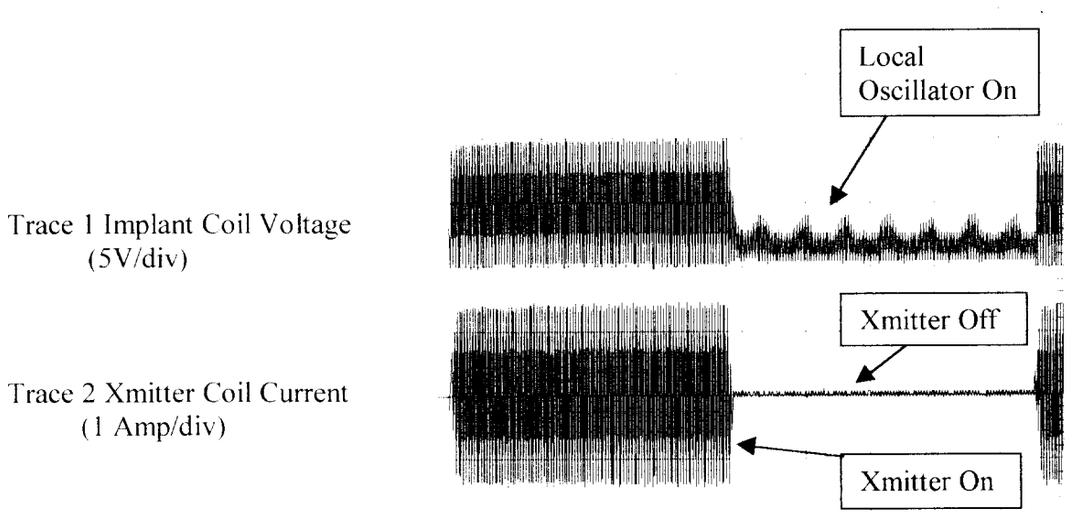


Figure 8 – Operation of Local Oscillator of MOS8, 150usec/horizontal division

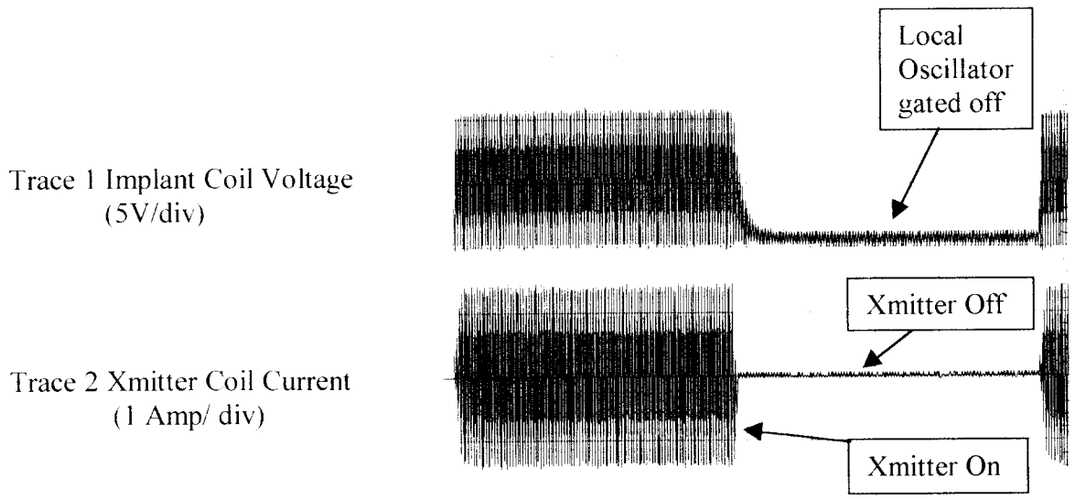


Figure 9 – Operation of MOS8 with Local Oscillator turned off, 150usec/horizontal division

Note that in Figures 7, 8, and 9, above, the somewhat "ragged" appearance of the traces is an artifact of the sampling oscilloscope used to store the data. Using an analog oscilloscope, the digital and analog signals are seen to be continuous and definitive.

We revised the rectifier/data demodulator of MOS8 for integration with the existing 2 MHz microstimulator circuitry. The existing external diode, amplitude demodulator, and clock recovery circuit were replaced by a new ASIC cell that uses the techniques of MOS8. Layouts for the revised and original 2MHz microstimulator appear in Figures 10 and 11, below. Presently these chips are under test.

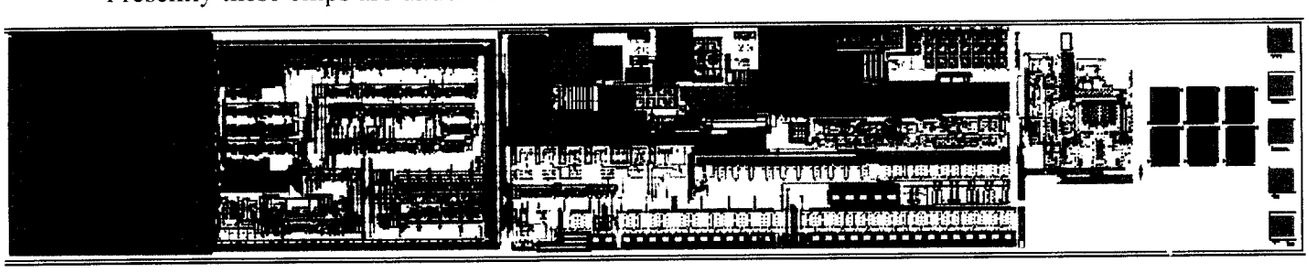


Figure 10 – 2MHz microstimulator with integrated rectifier and telemetry front end. *(Front End)*

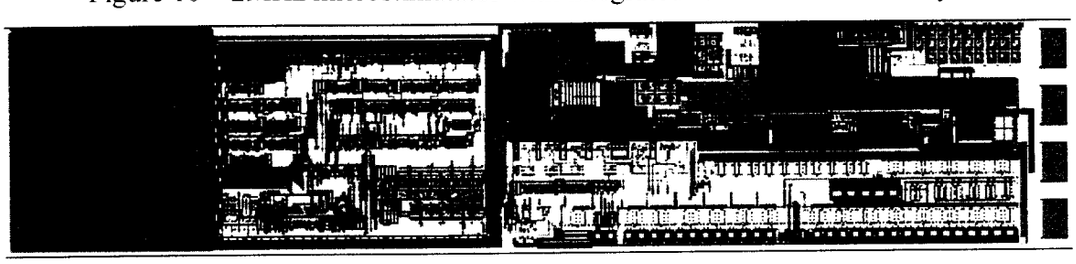


Figure 11 – Original 2MHz microstimulator that used external diode rectifier

Transmitter Design

The AM-modulated 2MHz transmitter was redesigned to satisfy two requirements: first, the 2 MHz microstimulator ASICs produced by the Mann Foundation required modulation that was close to square-shaped, as opposed to the triangular-shaped modulation produced by our first generation 2 MHz Class-E transmitters. Second, the original transmitter was difficult to build due to the use of many discrete components. The discrete components were used because the power Fets needed gate voltage of 8-12 volts. Therefore we had previously designed a high-speed 12-volt gate driver.

For this 2nd-generation design, we improved the sharpness in the AM-modulation by using digital edge control of the main Class-E switch. At the transition from high to low, the gate driver is turned off for 2 cycles, allowing the energy contained within the resonant power stage to dissipate. Once the coil current has dropped off to the desired level, the gate drive is turned back on with a reduced pulse width to maintain the low level of current. At the low-to-high transition, the duration of the gate drive is increased for 2-4 cycles in order to rapidly increase the stored energy within the resonant power stage. Once the desired high-level has been reached, the gate drive pulse width is reduced to maintain the coil current at the high level.

In this 2nd-generation design we used logic-level power Fets. This permitted the gates to be driven directly from high-speed AC-type logic. Thus, with the exception of the resonant circuit and the current feedback comparator, all components in this design are digital. A schematic of the revised transmitter design appears in Figure 12, below, and a full-size plot of the circuit board layout is shown in Figure 13, below. Presently we are building a supply of transmitters that are matched to various transmitter coil designs.

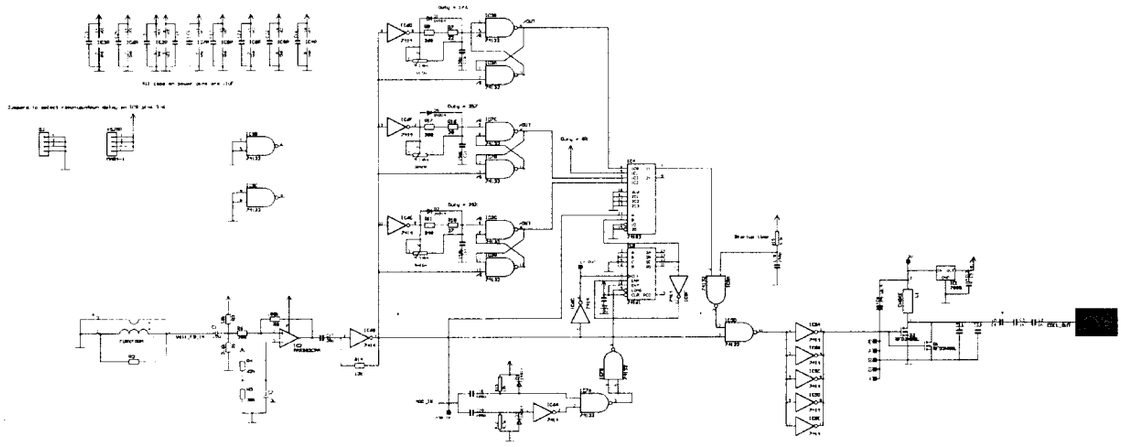


Figure 12 – Schematic of the 2nd-generation 2MHz transmitter circuit

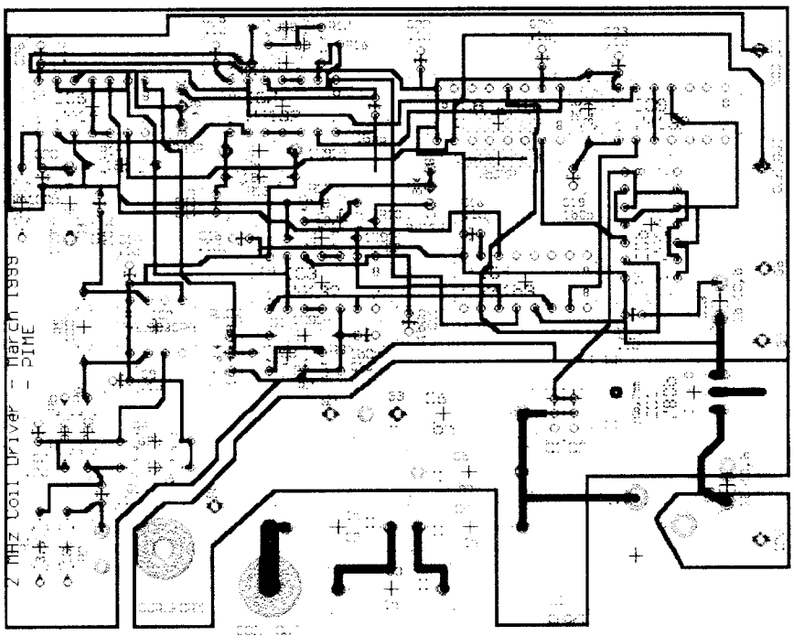
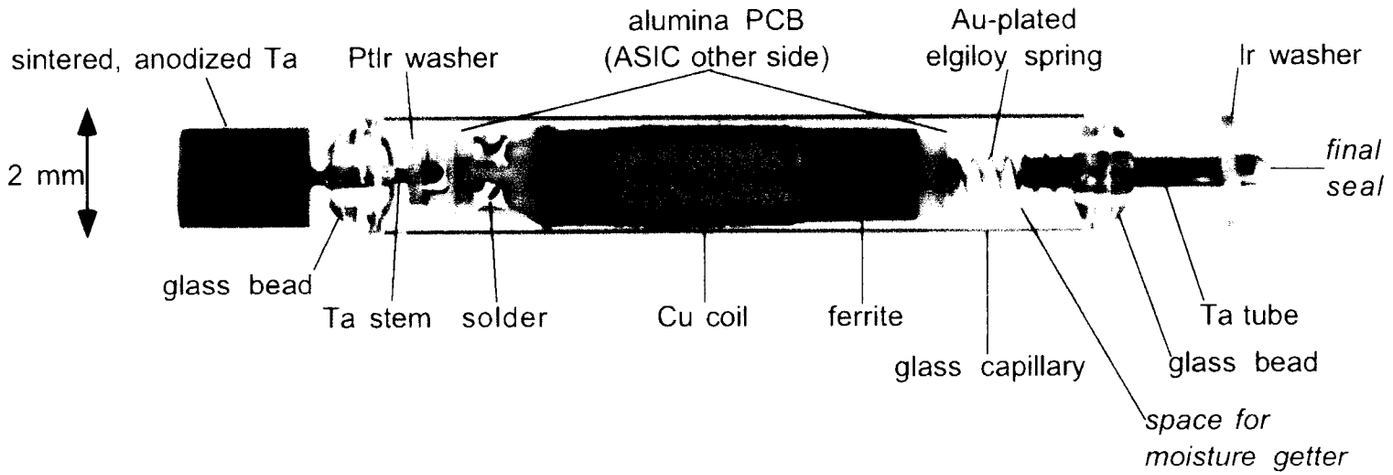


Figure 13 – Full size plot of circuit board for the 2nd-generation 2MHz transmitter

BION1:

2 MHz communications protocol
dual voltage AMI ASIC
ceramic hybrid assembly
glass package
capacitor electrodes

AB1102.cvs
Jan. 6, 1999
G.E. Loeb



Qualification Testing for BION1 System

Specific for Pilot Clinical Trial on Shoulder Subluxation at Queen's University

Plan approved January 13, 1999

Test results as of March 25, 1999

Report by Gerald E. Loeb, M.D., Principal Investigator

Purpose of Document

A detailed general product qualification process for Advanced Bionics was defined and approved previously. This document summarizes the subset of that process that is relevant to the limited scope of the proposed study, the current state of the testing and the remaining work to be completed as part of the internal qualification process and the regulatory submission package required from Queen's University before the first patient can be implanted.

Conditions of Trial

Venue of the Study

The study is being conducted by Queen's University in Kingston, Ontario. The senior investigators responsible for the study design and execution are Drs. Frances Richmond, Sandra Olney and Stephen Bagg. The study is funded by the Medical Research Council of Canada. The clinical protocol has been approved by the Human Investigational Review Board of Queen's University, conditional upon approval of the device by the Canadian Health Protection Branch, Therapeutic Products Program.

Manufacturer of Record

The implanted device and all external hardware and software are manufactured by Queen's University under the supervision of Dr. Gerald E. Loeb, a member of the clinical study team. The facility is operating under Good Laboratory Practice and Good Manufacturing Practice guidelines, including maintenance of device travelers and standard operating procedures for all critical assemblies and processes. An independent auditor (Pharmacon Research, Inc., Ottawa) has been retained as part of that regulatory process.

Conditions of Device Use

The study is limited to 20 patients. Each patient will be implanted with 2-6 devices within the first few weeks of recovery from a stroke that has unilaterally weakened the shoulder muscles. The implants are required to provide stimulation on a regular basis for a period of 6 weeks commencing 1 week after implantation. The stimulation periods will be less than 6 hours/day. The stimulation parameters can be anywhere within the rated output of the implants, as determined by the prescribing physician. The device implantation and programming will be performed by senior investigators who participated in the qualification testing. The inactive devices will be left in the patient after the completion of the study unless there are medical indications warranting their surgical removal.

Biocompatibility and Safety Considerations

Hazard Analysis and Test Justification - comprehensive plan developed in consultation with the Canadian Health Protection Branch and US FDA and documented in the appended BION Hazard and Risk Analysis plus various NIH Contract Proposals and Quarterly Progress Reports:

- ***Physical Anchoring - documented in refereed journal article***
- ***Mechanical Strength - documented in independent report of the Clinical Mechanics Group, Queen's University***
- ***Electrochemical Stability and Corrosion Tests - documented in refereed journal article and Quarterly Progress Reports of NIH Contracts***
- ***Passive Materials in vitro - documented in independent reports from Idexx***
- ***Passive Devices in vivo - documented in refereed journal article and independent reports from Idexx***
- ***Active Devices in vivo - documented in refereed journal article***
- ***Failsafe – design is inherently incapable of producing output that would be hazardous to tissue in any electronic failure mode of implant or external components, as documented in refereed journal articles and Quarterly Progress Reports of NIH Contracts***

Implant Reliability Considerations

Hazard and Failure Analysis and Test Validation - documented in Quarterly Progress Reports of NIH Contracts:

The following tests are in addition to the standard production tests that must be passed by all implants as summarized below (in sequential order):

- Ta open capsule hermeticity - no leak at limit of Alcatel sniffer test ($2x10^{-11}$ cc atm He/s)
- Vent tube hermeticity - no leak at limit of Alcatel sniffer test ($2x10^{-11}$ cc atm He/s)
- Final seal hermeticity - no leak at limit of Alcatel sensitivity for 25% He trapped in capsule ($2x10^{-10}$cc atm He/s)
- Anodization leak test - $<2\mu A$ @ compliance voltage, at completion of Ta anodization
- High pressure bomb test - 24 hr. in saline at room temperature with 160 atm pressure head of He

- Characterization test - place unit in saline in wet test well with rubber dam separating chambers with detecting electrodes, apply RF field with flat coil, command and record responses to all possible device addresses, record stimulus pulses for all output currents @ max pulse width, 10 pulse widths @ 10 mA, consistency of lock for 4 sets of 10 pulses each @ 10 mA, max pulse width, frequency following test for 100 pulse trains @ 10, 20, 50 and 100 pps.
- Dry well test (performed by physician at time of implant) - after autoclaving and while still in sterile package, confirm response to one and only one device address equal to address obtained during characterization test

- ***Package Hermeticity Process Reliability - performed on implants without moisture getter to increase sensitivity***

Chronic high pressure bomb test - *passed, continuing beyond 1 month*

This test is designed to demonstrate that the 24h bomb during 100% production testing effectively removes implants with flaws and that implants that have survived it have not been weakened by that test. Implants are removed from the high pressure bomb and inspected for cracks and visible moisture before repressurizing at weekly intervals during this test.

Chronic soak with temperature cycling and active pulsing - *passed, continuing beyond 6 months*

This test is designed to demonstrate that there are no interactions among materials and electronic function that cause unexpected failures. Acceleration factors include increased temperature, temperature cycling and continuous RF field and intense stimulation pulses. Similar testing has been used previously to demonstrate stability of package and electrode materials.

Chronic moisture sensing by impedance spectroscopy – *passed, continuing beyond 6 months*

This test is designed to demonstrate that hermetic seals that are not leaking at a level detectable during manufacturing tests are also not leaking at a much higher level of sensitivity. Special moisture sensing PCBs are built into the implants in place of the usual electronic subassembly (without getter) and the capsules are soaked continuously in water at 85°C. Before and at intervals during soaking, capsules are removed and tested for shifts in impedance vs. frequency by probing the output electrodes. Condensed or adsorbed water vapor in less than monolayer amounts should produce detectable changes in the spectroscopy curves.

- ***Electronic Function Tests - performed on implants with moisture getter and final ASIC and electronic subassembly***

<u>UNITS TESTED</u>: These tests have been successfully performed on BIONs with the low-voltage IC chip and electronic subassembly. Because they include potential failure modes related to the electronic subassembly rather than the package, they are now being repeated on BIONs build with the new IC chip and electronic subassembly. Results expected in April.

full characterization test

test material: completed implants after all production/sterilization

sample size: 5

test procedure: repeat production characterization test, making analog measurements from an oscilloscope for increased accuracy

acceptance criteria: <50% variance from nominal specifications, <20% variation between samples; absence of intermittent states over nominal range of RF field strengths from center to fringe of transmission coil.

temperature cycling

test material: completed implants after all production/sterilization

sample size: 5

test procedure: subject to active temperature cycling test (see details below) while monitoring continuously for 1 month

acceptance criteria: no visible cracks or moisture in implants, no electrical failures of implants, no significant change in pulse output characterization test (as defined below under Standard BION Test methods).

- ***Mechanical Reliability Tests***

<u>NOTE:</u> Where feasible, the same 5 BIONs were tested sequentially in each of the following tests rather than using fresh units for each test. This greatly increases the cumulative stress on the package and the significance of passing.

capsule strength, actual implant conditions

test material: completed BION capsules (may have dummy electronics)

sample size: 5

test procedure: push implant into fresh meat parallel to fascicle axis, record axial force required to extrude from insertion tool sheath while resisting sheath withdrawal manually. Retrieve implant and conduct 24h high pressure bomb test.

acceptance criteria: no visible cracks or detectable moisture in capsule

UNITS TESTED: ***A035, A039, A064, A178, A184***

RESULTS: ***Force required to insert the BIONs averaged 225 g of force. All passed visual acceptance criteria. Functional testing: A184 - non-functional dummy package. A064 - non-functional dummy package. A035 - no significant changes in output. A039 - no significant changes in output. A178 - no significant changes in output.***

feedthrough strength, axial loading

test material: half capsule subassemblies of each feedthrough

sample size: 5 of each end

test procedure: mount half capsule in Alcatel helium leak detector using capillary o-ring fixture, apply vacuum and set detector for maximal sensitivity. Apply gradually increasing axial load to metal tube or stem while monitoring for detectable leak under continuous helium curtain. Subject subassembly to 24h high pressure bomb test; repeat axial loading to failure.

acceptance criteria: no detectable leaks up to twice the maximal axial force measured in the preceding test; no visible cracks or detectable moisture in capsule after bomb; failure at least three times the maximal axial force measured in the preceding test

UNITS TESTED: ***Six half capsules were fabricated using established procedures.***

RESULTS: ***No leak was detectable to a maximal compression force of >1200 g (limited by ability of test fixture to hold capsules without sliding from applied force). After 24h high pressure bomb, no leaks were detectable at >1200 g; unable to load to failure.***

feedthrough reliability, mechanical shock

test material: completed implants after all production/sterilization

sample size: 5

test procedure: While in sterile package, drop implant onto vinyl tile floor from height of 1m, repeating 10 times in various orientations. After removing from all packaging, drop implant onto surgical instrument tray (stainless steel) from height of 20 cm, repeating 5 times in various orientations. Subject implant to 24h high pressure bomb test; repeat pulse output characterization test.

acceptance criteria: no visible cracks or detectable moisture in capsule after bomb; no significant change in output characterization test.

NOTE: This test differs from MIL-STD-883 because it is designed to simulate worst case mechanical handling during transportation and surgical handling rather than to document the actual resistance of the implant itself to known mechanical forces.

UNITS TESTED: ***A035, A039, A064, A178, A184***

RESULTS: ***All units intact; no condensation; no cracks detected.. A184 – non-functional dummy package. A064 – non-functional dummy package. A035 - no significant changes in output. A039 - address shifted; output improved. A178 - no significant changes in output except signal ratio dropped from 96% to 83%.***

thermal shock and sterilization cycling

test material: completed implants after all production/sterilization

sample size: 5

test procedure: Place packaged units in refrigerator at 0°C for 1 hour and then through standard steam autoclave; repeat for total of 5 cycles. Remove from packaging and subject to 24h high pressure bomb test; repeat pulse output characterization test.

acceptance criteria: no visible cracks or detectable moisture in capsule after bomb; no significant change in pulse output

NOTE: This test differs from MIL-STD-883E because it is intended to simulate a worst case actual thermal shock and thermal cycling (transportation of packaged units and multiple resterilization in such packaging) rather than to document the actual resistance to thermal stress of the implant itself, which is irrelevant under the isotemperature working conditions in the body.

***UNITS TESTED**: A035, A039, A064, A178, A184*

***RESULTS**: All units intact; no condensation; no cracks detected. A035; no significant changes in output except one dropout point in the pulse width test. A039; no significant changes in output. A178; no significant changes in output.*

External System Reliability Considerations

Bedside Controller Function - existing units aceptable by virtue of continuous use in chronic test facility over past year; failure modes are nonfunctional rather than hazardous to patient

Application Specific Coil/Driver Function - 1 mo. active continuous use to be performed when new design provided by IIT

Component Interchangeability

test material: completed implants after all production/sterilization; existing bedside controllers and new coil/drivers

sample size: 5 implants, 3 coil drivers, 5 bedside controllers, 2 PCs

test procedure: at each interaction level, confirm ability to perform normal function with all combinations of components.

acceptance criteria: All 5 implants can be driven by all 3 coil drivers over the full specified range of distances, all 5 bedside controllers will successfully communicate with all 3 coil drivers, both PC systems will run ClinFit and communicate successfully with all 5 bedside controllers

UNITS TESTED: general interchangeability demonstrated informally during development and qualification testing phase. Specific testing per above procedure awaiting delivery of new coil-drivers from IIT, due in April.

Key Component Qualification Tests

ASIC & Electronic Subassembly Function - to be determined and performed by vendor (AEMF)

Standard BION Test Methods Incorporated by Reference

Characterization Test

Complete details available in BION Tester Manual. Device is mounted in the wetwell fixture, which separates its two output electrodes by a rubber dam, immersing each in a saline well fitted with a platinum-iridium recording electrode. Stimulation and recharge current is measured across a 100 ohm precision resistor between the recording electrodes, using an oscilloscope and/or by digitizing circuitry built into a modified bedside controller. This is presently configured as a screening test, with limited accuracy and precision. Experience has shown that the actual output pulses depend almost entirely on the characteristics of the ASIC circuits, which are somewhat difficult to predict but highly uniform for all ASICs from a given foundry run. Failures rarely involve drift of these parameters; instead, problems manifest as complete loss of output, intermittent output, sensitivity to RF field strength, or gross deviations from requested output pulses. The absence of such significant changes is deemed to be a passed test.

Active Temperature Cycling Test

Complete details available in QPRs. Each of up to 8 devices is mounted in a separate saline-filled vial equipped with pulse current recording electrodes and monitored by PC similarly to the Characterization Test. All mounted devices are stimulated continuously with 50 pps @ 10 mA x 258 μs. Temperature is controlled and recorded by thermocouple and cycled continuously between 37°C (3 hours) and 77°C (9 hours), with less than 10 min per transition. The current amplitude and pulse width of single pulses are recorded hourly and a complete characterization test is recorded at the end of each 12h temperature cycle.

High Pressure Bomb Test

Up to 16 devices are placed in epoxy wells filled with saline at room temperature. The well assembly slides into a metal enclosure which is pressurized with the unregulated pressure from a fresh helium tank (typically 2200 - 2600 psi). After the test period, pressure is released gradually and devices are removed from the wells and inspected for visible cracks while rotating manually under a dissecting microscope with oblique lighting and for visible water or condensed moisture when cooled by swabbing with methanol.